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Deletion of Chromosome 21 in a Girl With Congenital Hypothyroidism and Mild Mental Retardation

B. Edman Ahlbom, R. Sidenvall, and G. Annerén

Department of Clinical Genetics, University Hospital, Uppsala (B.E.A., G.A.); and Department of Paediatrics, Central Hospital of Hudiksvall, Hudiksvall (R.S.), Sweden

We report on a girl with a large interstitial deletion of the long arm of chromosome 21 and with mild mental retardation, congenital hypothyroidism, and hyperopia. The deletion [del(21)(q11.1–q22.1)] extends molecularly from marker D21S215 to D21S213. The distal breakpoint is not clearly defined but is situated between markers D21S213 and IFNAR. This patient has the largest deletion of chromosome 21 known without having severe mental retardation or malformations. The deletion does not involve the "Down syndrome chromosome" region, the region of chromosome 21 which in trisomy causes most of the manifestations of Down syndrome. Apparently, the proximal part of the long arm of chromosome 21 does not include genes that are responsible for severe clinical effects in the event of either deletion or duplication, since several reported patients with either trisomy or deletion of this region have mild phenotypic abnormalities. Congenital hypothyroidism is much more common in Down syndrome than in the average population. Thus, the congenital hypothyroidism of the present patient might indicate that there is one or several genes on the proximal part of chromosome 21, which might be of importance for the thyroid function. © 1996 Wiley-Liss, Inc.

KEY WORDS: chromosome 21 deletion, mental retardation, congenital hypothyroidism

INTRODUCTION

Chromosome 21 is the smallest human chromosome and contains about 1.7% of the human genome. Down syndrome (DS) is the most common diagnosis in patients with mental retardation and is caused by trisomy 21. The molecular bases of the associated defects in DS and the biology of these defects are unclear. One region of the long arm of chromosome 21 close to marker D21S55 seems to be essential for expression of the DS phenotype. This "DS chromosome region" probably contains the major genes, which when present in three copies, cause the phenotype of DS [Epstein, 1986]. In order to elucidate the genetic background of DS, it is important to carefully define the clinical manifestations as well as the molecular abnormality in patients with structural aberrations of chromosome 21, both duplications and deletions.

The aim of the present investigation was to study the clinical traits of a girl with an extensive interstitial deletion of the long arm of chromosome 21 and to define the lesion cytogenetically and molecularly.

CLINICAL REPORT

The patient, a 12-year-old girl, is the second child of healthy, unrelated parents. The family history is negative concerning mental retardation and thyroid disorders. At the time of her birth, father was 33 years old and mother 28 years old. The height of the mother and father was 1.84 m and 1.80 m, respectively. The pregnancy was normal and the patient was born after 41 weeks of gestation. Birthweight was 3.4 kg and birthlength was 0.48 m. Noted at birth were muscular hypotonia, a large tongue, and a shrill cry. Congenital hypothyroidism was found and thyroxin treatment was begun at the age of 11 days. She had a refraction error with +7D in both eyes and has had glasses since the age of 2 years. Motor and mental development has been slightly retarded: she was able to walk at 15 months and to say the first words at 11 months. However, her verbal performance has not developed well. She has severe articulation problems and has had speech therapy since the age of 3 years. She has been able to attend a normal school, but with extra support. According to the

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Address reprint requests to Dr. G. Annerén, Department of Clinical Genetics and Pediatrics, University Hospital, S-751 85 Uppsala, Sweden.

WISC performance test she had an I.Q. of 65 at the age of 7 years. She had primary nocturnal enuresis until the age of 9 years. Growth velocity was normal during the first 2 years but has increased since then. Her height at 2, 5, and 8 years was 0.88 m (±0 SD), 1.20 m (+2.5 SD), and 1.43 m (+3 SD), respectively (Swedish standard, Karlberg et al., 1976). At the age of 10 years she showed signs of early puberty and was admitted to the Department of Pediatrics of the University hospital of Uppsala. At the age of 10 years the skeletal maturation was advanced, with a skeletal age of 13 years according to Greulich and Pyle [1959] and TW2 [Tanner et al., 1985]. Her physical appearance differs from that of her parents and her brother. Physical examination at the age of 10 years showed the following (Fig. 1): slight obesity with a weight of 49 kg and a height of 1.56 m; and down-slanting palpebral fissures, a high-arched palate, prognathism, and a protruding lower lip. Ears were normal and the nasal bridge was prominent. She had normal external genitalia with a Tanner puberty stage of 2–3. Hands and feet were long and slender, with shortness and mild clinodactyly of the fifth fingers. Fingernails were normal. Neurological examination demonstrated ataxia, poor balance, and muscular hypotonia. Endocrinological evaluation showed elevated serum levels of FSH, LH and oestradiol, indicating puberty.

CYTOGENETIC ANALYSIS

Routine methods were used for chromosome preparation from blood and fibroblasts. G-banding with trypsin-Giemsa and prophase banding on chromosomes were performed according to standard methods.

Chromosome analysis was carried out on the patient and her parents' peripheral lymphocytes and also on fibroblasts from the patient. Chromosomes were analyzed in 50 cells from each individual.

MOLECULAR ANALYSIS

The extension of the cytogenetically visible deletion was defined by analyzing genomic DNA with highly polymorphic DNA markers (the alleles consisting of variable numbers of di-, tri-, or tetranucleotide repeats) located on chromosome 21 [Petersen et al., 1990, 1991]. For each marker, the allelic pattern corresponding to the patient was compared with that of her parents.

Genomic DNA from the patient, her parents, and from normal controls was purified from blood by standard procedures. The DNA markers were analyzed by polymerase chain reaction (PCR): 10 ng of genomic DNA was amplified in a total volume of 10 μl consisting of 1.5 mM $MgCl_2$, 50 mM KCl, 10 mM Tris, 0.01% gelatin, 200 μM dNTPs, 0.1 μM of each primer, and 0.5 U Taq polymerase. One primer was radiolabeled with T4 kinase [Sambrook et al., 1989]. The PCR program used was 1× (95°4 min, 55°30 sec, and 72°30 sec), 26× (95°30 sec, 55°30 sec, and 72°30 sec), and 1× (95°30 sec, 55°30 sec, and 70°4 min). The PCR products were separated on a denaturing 6% polyacrylamide gel, and the dried gel was exposed to X-ray film for 12 to 24 h. The polymorphisms studied were D21S215, D21S120, D21S258, D21S16, D21S189, D21S172, D21S11, D21S145, D21S232, D21S210, D21S217, D21S226, D21S213, D21S216, IFNAR, D21S167, HMG14, D21S212, PFKL, and D21S171. The location of these markers on chromosome 21 can be found in the report by McInnis and co-workers [1993], except for D21S189 [Van Camp et al., 1991].

RESULTS

Cytogenetic analysis of the patient showed a de novo interstitial deletion of the long arm of chromosome 21:

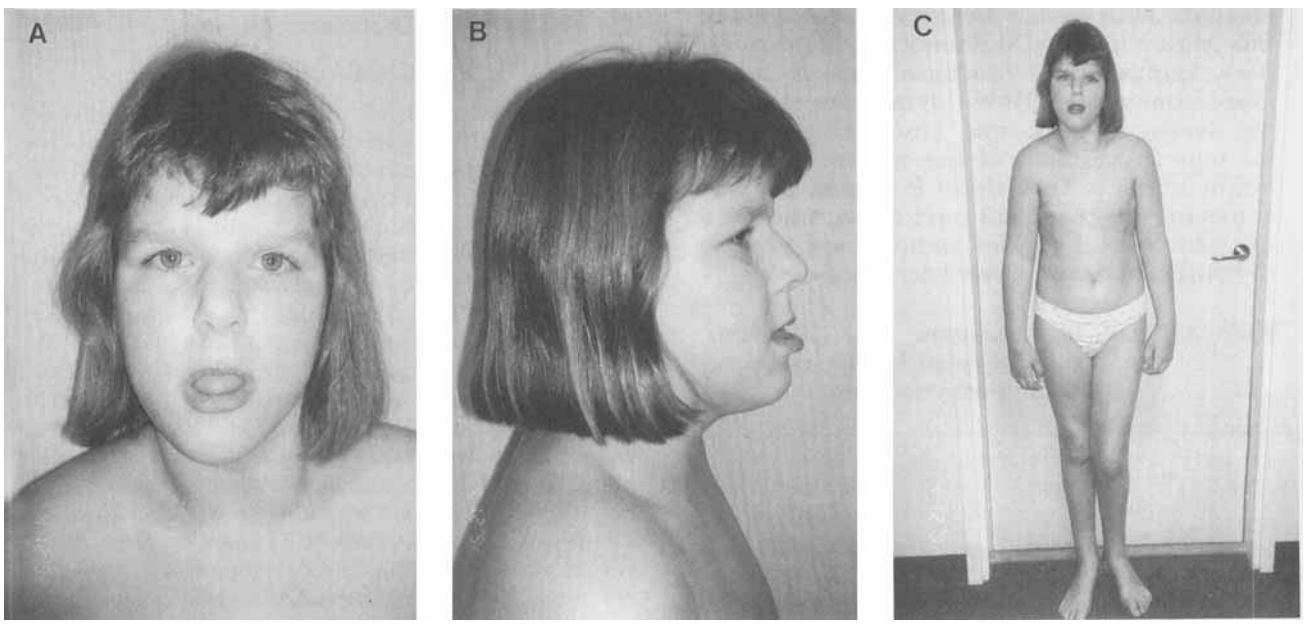

Fig. 1. **A,B,C:** The patient at the age of 10.5 years.

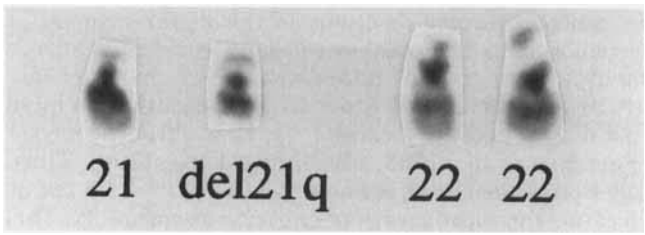

Fig. 2. G-banded chromosomes 21 and 22 of the patient, showing the interstitial deletion: del(21)(q11.1–q22.1).

46,XX,del(21q11.1–q22.1) (Fig. 2). Both parents have a normal karyotype.

Molecular analysis of the allelic pattern for each marker demonstrated that at 5 of the 20 marker loci analyzed, the patient had lost one parental allele. In all five cases, D21S215, D21S16 (Fig. 3), D21S11, D21S217, and D21S213, the father's allele was lost. The other markers analyzed located between D21S215 and D21S213 were uninformative, as was D21S216 located between D21S213 and IFNAR. At the IFNAR locus, the patient is heterozygous. The patient thus has a paternally derived interstitial deletion of chromosome 21 extending from D21S215 to D21S213 with the distal breakpoint between D21S213 and IFNAR (Fig. 4 and Table I).

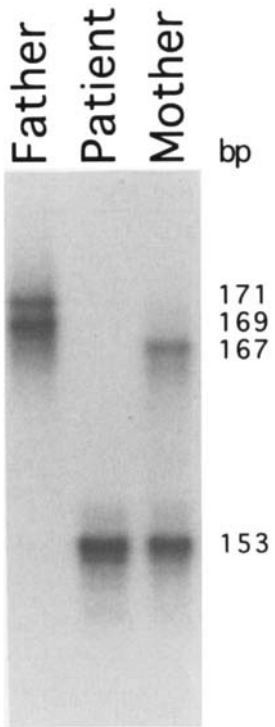

Fig. 3. Autoradiogram of PCR analysis of the polymorphic marker D21S16, showing that the patient has inherited only the 153 allele from her mother, thus having a paternal deletion (the father has alleles 169 and 171 and the mother has alleles 153 and 167).

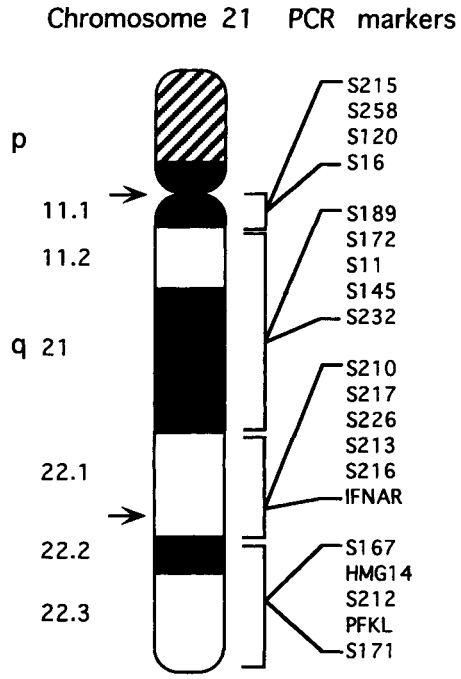

Fig. 4. Chromosome 21 with approximate positions of the markers analyzed in the study. The arrowheads mark the approximate positions of the breakpoints of the deletion, del(21)(q11.1–q22.1).

DISCUSSION

A girl with a large interstitial deletion of the long arm of chromosome 21 is presented. Despite the extent of the deletion, the clinical manifestations are relatively mild. The facial appearance is similar to that of some previously presented patients with deletions in the same region of chromosome 21 [Modi and Buckton, 1982; Wulfsberg et al., 1983; Roland et al., 1990; Korenberg et al., 1991]. The phenotypic findings of patients with molecu-

TABLE I. Chromosome 21 PCR Polymorphisms: Genotypes of the Patient and Her Parents

Locus	Father	Child	Mother
D21S215	1,3	−,2	2,1
D21S258	2,1	−,1 (or 1,1)	1,1
D21S120	2,3	−,3 (or 3,3)	3,1
D21S16	3,4	−,1	1,2
D21S189	1,1	−,1 (or 1,1)	1,1
D21S172	3,2	−,2 (or 2,2)	2,1
D21S11	2,3	−,4	4,1
D21S145	1,2	−,2 (or 2,2)	2,2
D21S232	1,2	−,2 (or 2,2)	2,2
D21S210	1,2	−,2 (or 2,2)	2,3
D21S217	1,1	−,2	2,1
D21S226	2,1	−,1 (or 1,1)	1,1
D21S213	2,2	−,1	1,1
D21S216	2,1	−,1 or 1,1	1,2
IFNAR	2,4	4,3	3,1
D21S167	3,2	2,4	4,1
HMG14	1,1	1,1	1,1
D21S212	4,2	2,1	1,3
PFKL	1,3	3,1	1,2
D21S171	2,3	3,2	2,1

larly defined deletions of the region 21q11–q22.1 are presented in Table II (the cases described by Modi and Buckton [1982] and Wulfsberg et al. [1983] are not included since they are not molecularly analyzed).

This patient has the largest deletion of chromosome 21 known without having severe mental retardation or malformations. The deletion does not involve the distal part of the long arm of chromosome 21, where the genes responsible for most of the DS phenotype are located; still it is surprising that such a large deletion of an autosomal chromosome has such a small impact on the phenotype. There is one previously described patient with a proximal deletion of chromosome 21 and moderate mental retardation and multiple congenital malformations [Reynolds et al., 1985]. No molecular analysis was performed in this patient, but on the cytogenetic evidence it seems that the deletion extended further distally on the long arm of chromosome 21 than the deletion of the patient presented here. Also several patients are described with proximal deletions of 21q due to unbalanced translocations [Holbek et al., 1974; Phelan et al., 1988; Viljoen et al., 1992; Hertz et al., 1993; Courtens et al., 1994]. Most of these patients are severely affected with mental and growth retardation and congenital anomalies. However, since they also have monosomy for parts of another chromosome involved in the translocation, it is difficult to decide if the manifestations are caused by the chromosome 21 deletion or not.

Monosomy of the most distal part of the long arm of chromosome 21 (distal 21q22.3) have been reported to result in few phenotypic effects [McGinnis et al., 1992]. In contrast, larger deletions of the distal segment of chromosome 21 (21q22.1-qter) seem to result in severe mental and growth retardation [Yamamoto et al., 1979], and this is also reported for patients with large distal 21q deletions caused by ring chromosome 21 [Ferrante et al., 1983; McGinnis et al., 1992]. Thus, deletion of the chromosome region 21q22.1–22.2 seems to cause the most severe phenotypic abnormality. This segment is also known as the "DS chromosome region," and for this reason it is important to define all the genes within this region and to understand their function in order to establish the background of DS.

The present patient has congenital hypothyroidism, which was not previously described in patients with deletion of chromosome 21. The hypothyroidism in our patient might be a coincidental finding, unrelated to the chromosome 21 abnormality. On the other hand, the finding could be of interest, since patients with DS often suffer from thyroid disorders [Sare et al., 1978], and congenital hypothyroidism is much more common in DS than in normal individuals [Cutler et al., 1986]. One or several genes that might be involved in the development and function of the thyroid gland could be located on the proximal part of the long arm of chromosome 21.

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TABLE II. Clinical Manifestations in Patients With Partial Deletion 21 Investigated With Cytogenetic and Molecular Methods*

	Roland et al. [1990]		Korenberg et al. [1991]	Present case
	Case 1	Case 2		
Deletion (locus)	q11.2→q21.3 (D21S51–S22)	q11.2→q21.3 (D21S51–S22)	q11.2→q21.3 (D21S16–APP)	q11.1→q22.1 (D21S215–S213)
Birthweight (g)	2,325		2,355	3,400
Mental retardation	Mild	Mild	−	Mild
Motor function impaired			+	Mildly
Short stature	+	+	−	−
Obesity	+	+	−	Slight
Muscular hypertonia	−	−		−
Muscular hypotonia				+
Prominent forehead	+			+
Epicanthic folds	−	−		−
Downslanting palpebral fissures	−	−	+	+
Large/low set ears	+	+	+	−
High arched palate	+	−	+	+
Prominent nose/nasal bridge	+		−	+
Prognathism	−			+
Downturned corners of mouth	−	−	+	−
Long/slender hands	+	−		+
Clinodactyly of 5th finger			+	+
Short 5th finger	+	+		+
Broad feet	+	+		−
Pes planus	+			−
Large stiff joints	+	+		−
Abnormal genitalia			Small testes	−
Pubertas praecox	−			+
Congenital hypothyroidism	−	−	−	+

* +, Sign present; −, sign absent.

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